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| 09/498,046 | 02/04/2000 | Sabine Neirynck | VIB-08 | 8244 |

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| EXAMINER | |
|---|---|
| CHEN, STACY BROWN | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/498,046 | NEIRYNCK ET AL. | |
| | Examiner | Art Unit | |
| | Stacy B. Chen | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *26,31,32,34,36-41,46 and 52-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,31,32,34,36-41,46 and 52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment and response filed June 19, 2008 is acknowledged and entered. Claims 26, 31, 32, 34, 36-41, 46 and 52-61 remain pending and under examination.

### *Response to Amendment*

2. The objection to claim 55 is withdrawn in view of Applicant's amendment.

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 26, 31, 32, 36, 38, 41, 46, 53-55 and 58-61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al.* (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"). Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that the motivation to combine the teachings of Pumpens with Slepushkin is inadequate. Particularly, Applicant argues that the statement by Slepushkin concerning the vaccinia-M2 recombinants being unable to provide protection in mice is not motivation to combine Slepushkin's M2 with Pumpens HBc carrier. Applicant reasons that Slepushkin did demonstrate protection from influenza with the M2

composition, thus overcoming the problems of the prior art; therefore, there would have been no apparent motivation to further modify the M2 composition of Slepushkin.

- Applicant also argues that there would not have been motivation to change from using the vaccinia carrier system (mentioned in Slepushkin as problematic in terms of M2 immunogenicity) for the HBc carrier system because so much more work has been done with vaccinia than HBc. Applicant provides the search results of a query in a search engine showing that the number of hits relating to "vaccinia recombinant vaccine" and "HB core recombinant vaccine" were 964,000 and 516,000 hits, respectively.
  - In response to Applicant's arguments, the obviousness rejection follows this logic: Pumpens discloses HBc carriers that are useful as epitope carriers. Pumpens does not specifically name the influenza A M2 antigen. However, Slepushkin discloses influenza A M2 antigen and also teaches that there are problems with protective immunity when using the M2 antigen in certain contexts, such as the vaccinia-M2 recombinants. Therefore, given the problems associated with inducing an effective immune response using M2, it would have been obvious to use a system of presenting M2 to the immune system that would enhance its immunogenicity. Slepushkin found that partially purified baculovirus-expressed M2 worked, but that is not the only way to increase the immunogenicity of M2 available in the art. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference. Considering Pumpens teachings regarding the advantages of using HBc carriers, one would have been motivated to increase the immunogenicity of M2 by using the HBc carrier.

- With regard to the comparison of the search results for vaccinia versus HBc carrier, the Office does not consider this argument to be persuasive. Degrees of popularity do not determine obviousness.

- Applicant argues that Slepushkin suggests the use of the full-length M2 protein, whereas the instant invention employs an extracellular part of M2 (M2e).
  - In response to Applicant's argument, the claims are not limited to an extracellular part of M2. The claims recite, "fusion product comprising (i) an antigen that is an immunogenic extracellular part of (a) an M2 membrane protein of human influenza A virus". In view of the term "comprising", which is open claim language, the claims are not limited to the embodiment that Applicant may be intending. Furthermore, even if the claims were limited to the extracellular part of M2, it would have been obvious to use the extracellular part of this protein because it is more exposed to the immune system than the intracellular part of the protein. An immune response to the extracellular portion of the protein would be expected to be more valuable than an immune response to the intracellular part which is not readily exposed naturally. It would have been well within the ability of the ordinary artisan to determine the extracellular part of the protein.

5. Claim 37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"), as applied to claim 26, and further in view of Highfield *et al*. (AU-B-49273/90, "Highfield", cited in IDS filed 11/26/07).

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant's arguments regarding the combination of Pumpens and Slepushkin are addressed above. Applicant additionally argues that even if the combination of Pumpens and Slepushkin were obvious, Highfield's teaching that a fusion construct can be expressed from any acceptable cell line is quite different from the expression that leads to the fusion product of claim 26 being anchored in the membrane of an acceptor cell expressing the fusion product, as claimed. Applicant asserts that there is no evidence on the record that every protein that is expressed in any acceptable cell line is automatically transported to and anchored in the cell membrane.
  - In response to Applicant's argument, the expression of the HBc/M2 construct from a cell line is expected to result in a fusion product anchored in the membrane of that cell. The reason for this expectation is that the components of the invention (HBc/M2) are the same as those suggested by the prior art, thus the outcome is expected to be the same as Applicant's teachings. The claims are not limited to any particular cell type, and M2 protein is known to be a transmembrane protein (as taught by Slepushkin). Transmembrane proteins are expected to anchored in the cell membrane from which cells they are expressed.

6. Claims 34 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"), as applied to claim 26, and further in view of Highfield

*et al*. (AU-B-49273/90, "Highfield") and van de Guchte *et al*. (*Applied and Environmental Microbiology*, 1989, 55(1):224-228, "van de Guchte"). Claims 34 and 39 require that the immunogenic composition comprise *Lactococci* cells expressing the fusion product in or on their cell membrane or cell well. Applicant's arguments have been carefully considered and have been addressed above.

7. Claims 40 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin"), as applied to claim 26, and further in view of Kedar *et al*. (U.S. Patent 5,919,480, filed June 23, 1997, "Kedar"). Applicant's arguments have been carefully considered and have been addressed above.

8. Claims 26, 31, 32, 36, 38, 41, 46, 53, 54 and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens (*Intervirology*, 1995, 38:63-74, "Pumpens") in view of Slepushkin *et al*. (*Vaccine*, 1995, 13(15):1399-1402, "Slepushkin") as applied to claims 26, 31, 32, 36, 38, 41, 46 and 53-55 above, and further in view of Sunstrom *et al*. (*J. Membrane Biol*. 1996, 150:127-132, "Sunstrom", already of record) or Hongo *et al*. (*Journal of Virology*, April 1997, 71(4):2786-2792, "Hongo").

- Applicant's arguments have been carefully considered and have been addressed above. Applicant additionally points to Sansom et al. (PEDS, 1993, 6(1):65-74), which basically elucidates the amino acid residues that are associated with the transmembrane portion of

the M2 ion channel. Applicant argues that the claims are limited to an extracellular part of M2 while the prior art is limited to the entire protein.

- As discussed above, the claims are not limited to the extracellular part of M2, NB or CM2 because of the open claim language "comprising". Furthermore, even if the claims were limited to the extracellular part of M2, NB or CM2, it would have been obvious to use the extracellular part of these proteins because they are more exposed to the immune system than the intracellular part of the proteins. An immune response to the extracellular part of these proteins would be expected to be more valuable than an immune response to the intracellular part of these proteins which are not readily exposed naturally. It would have been well within the ability of the ordinary artisan to determine the extracellular part of the protein.

***Conclusion***

9. No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/
Primary Examiner, TC1600